PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Initial characteristics and course of disease in patients with suspected COVID-19 managed in general practice: a prospective, multicentre cohort study
AUTHORS	PHAN, Tan-Trung; Mirat, William; Brossier, Sophie; Boutin, Emmauelle; Fabre, Julie; Hoonakker, Jean-Denis; Bastuji-Garin, Sylvie; Renard, vincent; ferrat, emilie

VERSION 1 – REVIEW

REVIEWER	Nehme, Mayssam Hôpitaux Universitaires de Genève, Primary Care Division
REVIEW RETURNED	17-Oct-2022

GENERAL COMMENTS	The authors present an interesting paper on the prevalence of post-COVID symptoms during the first pandemic wave in an outpatient setting with GP visits. This is new compared to studies in outpatient settings without GP visits, and studies in inpatient settings. However some elements need to be reviewed: Major comments: 1. It is unclear how asthenia and other symptoms were defined, a supplement with the questions or elements of the GP assessment would be necessary in order to understand what is the definition of asthenia and other symptoms. This in turn could affect the prevalence of these symptoms in each group. 2. If most symptoms were self-reported as is probably the case, this should be added as a limitation 3. Another limitation is the small sample size when comparing persistent symptoms at 3 months. Conclusions comparing the prevalence of persistent symptoms could not be drawn (Table 2; asthenia n=9 vs 6; cough n=3 vs 4 etc.) and should be removed or mitigated when mentioned in the manuscript. 4. It is unclear what the multivariate analyses were adjusted for, this should be added. Additionally some of the 95%CI are quite large suggesting a very small sample size. These calculations are not reliable. Minor comments: 1. English language should be rechecked (for example: extrapolable -> extrapolated; presential (table 1) -> in-person) 2. In the discussion, authors mention: « It appears that COVID-19 is a relapsing-remitting disease" This sentence is not accurate, we

	now know that there are post-acute sequelae of SARS-CoV-2 but this does not mean that COVID-19 is a relapsing-remitting disease

REVIEWER	Blacketer, Clair Janssen Research and Development LLC
REVIEW RETURNED	04-Jan-2023

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. It is well-presented and clearly demonstrates the author's intent to understand the persistence of COVID-19 symptoms in a GP patient population. I recommend this article to be accepted with a few minor revisions: 1. In the abstract and background, I was initially confused at the description of the patient population. It is presented as "...patients with suspected COVID-19 managed by GPs (confirmed cases, no-COVID cases, and uncertain cases)...". I did not immediately understand that the patients suspect themselves of a COVID-19 infection who then present to a GP who ultimately determines the patient's COVID-19 status after ordering one of the three tests described in the methods. I suggest re-wording this definition slightly to clarify the cohort of patients used in this study. 2. In the methods, the description of how COVID-19 status was determined is concerning because the patients are all recruited between March and May of 2020 which is when both the RT-PCR and serology tests were not widely available. As a reader, this called into question how the patients were grouped into confirmed COVID, no COVID, and uncertain COVID, even with the caveat that serology tests were administered a posteriori. Please include a description or table showing how many patients had each test for COVID-19, whether they were positive or negative, and what subgroup they were assigned to. 3. The first line of the discussion is misleading: "During the first wave of COVID-19 in France....". It suggests that all patients in France with suspected COVID-19 were included in the study. Please reword for clarity in relation to study that was performed.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comments to the Author:
The authors present an interesting paper on the prevalence of post-COVID symptoms during the first pandemic wave in an outpatient setting with GP visits. This is new compared to studies in outpatient settings without GP visits, and studies in inpatient settings. However some elements need to be reviewed:
Reply:
We thank the reviewer for this comment.

Major comments:
1. It is unclear how asthenia and other symptoms were defined, a supplement with the questions or elements of the GP assessment would be necessary in order to understand what is the definition of asthenia and other symptoms. This in turn could affect the prevalence of these symptoms in each

group.
Reply:
The patient's persistent symptoms were recorded during a visit to the GP or a during phone call between the patient and the GP. No definition was given to the GPs, who determined – as in their usual practice- whether the patient was cured or not, and which symptoms persisted. We agree that these aspects were not very clear in the manuscript, so we have modified the outcomes paragraph, as follows: "The GP identified and recorded the patient's persistent symptoms (if any), according to his/her usual clinical practice. We asked the GPs three questions: "Do you consider that the patient has been cured?", "If not, which symptoms persisted?", and "Do you attribute those symptoms to the initial disease?". Persistent symptoms (if any) were not rated on a scale or using a questionnaire." (page 7)

To take account of a potential impact on the prevalence estimates, we have modified the limitations section, as follows: "The methods for determining the presence or absence of persistent symptoms were left to the GP's discretion; the use of particular questionnaires or scales was not imposed on them. This lack of standardization might have influence the estimated prevalence of persistent symptoms. However, this unconstrained type of assessment was similar to that used in the GPs' routine clinical medical practice." (page 13)

2. If most symptoms were self-reported as is probably the case, this should be added as a limitation
Reply:
The symptoms were not really self-reported by the patient; they were identified and recorded by the GP, as in his/her routine clinical practice.

3. Another limitation is the small sample size when comparing persistent symptoms at 3 months. Conclusions comparing the prevalence of persistent symptoms could not be drawn (Table 2; asthenia n=9 vs 6; cough n=3 vs 4 etc.) and should be removed or mitigated when mentioned in the manuscript.
Reply:
To account for this comment, we modified the following sentences:
1/ of the abstract (page 2): "Confirmed cases were more likely to have persistent symptoms than no-COVID cases (P=0.09), were more likely to have anosmia (P=0.047) and other rare symptoms (P=0.071);

2/ of the Results: "The confirmed COVID group was more likely to have persistent anosmia (OR=8.51; 95% CI [1.03-70.43]) and other miscellaneous symptoms (deep vein thrombosis, alopecia, palpitations, myalgia, feeling feverish, and memory impairments) (OR=7.02; 95% CI [0.84-58.29])." (page 10)

3/ of the Discussion: "Given the small number of patients with persistent symptoms, the corresponding results should be interpreted with caution (especially the ORs with very broad CIs)" (pages 12-13).

4. It is unclear what the multivariate analyses were adjusted for, this should be added. Additionally some of the 95%CI are quite large suggesting a very small sample size. These calculations are not reliable.
Reply:
We agree with the Reviewer and so have added legends to Table 3 ("the multivariate model included the following variables: fever or feeling feverish and anosmia") and Table 4 ("the multivariate model included the following variables: age > 70 and/or presence of at least one comorbidity, number of systemic symptoms and abnormalities in a lung examination").
We agree that the sample size used to analyze persistent symptoms was small. Thus, to reinforce the

validity of our estimates (the ORs [95% CIs] in Tables 3 and 4), we generated some exact logistic models. Given that the results obtained (see the “tables for the reviewers” at the end of this letter) are very similar to those of Tables 3 and 4, we consider that our calculations are reliable. Nevertheless, and as mentioned above, we now mention in the manuscript that because of the small number of patients with persistent symptoms, these results should be interpreted with caution (especially the ORs with very broad CIs) (page 13).

Minor comments:
1. English language should be rechecked (for example: extrapolable -> extrapolated; presential (table 1) -> in-person)
Reply:
The manuscript has been copy-edited by a native English speaker (PhD in Biochemistry). We believe that any remaining points will be related to personal preference and writing style, rather than grammar, idiom, or clarity.

2. In the discussion, authors mention: « It appears that COVID-19 is a relapsing-remitting disease” This sentence is not accurate, we now know that there are post-acute sequelae of SARS-CoV-2 but this does not mean that COVID-19 is a relapsing-remitting disease
Reply:
We agree and we thank the Reviewer for this comment. Hence, we have modified the sentence, as follows: “It has been widely reported that patients can experience persistent symptoms more than four weeks after an episode of COVID-19 [36]. » (page 14)

Reviewer: 2
Mrs. Clair Blacketer, Janssen Research and Development LLC
Comments to the Author:
Thank you for the opportunity to review this manuscript. It is well-presented and clearly demonstrates the author's intent to understand the persistence of COVID-19 symptoms in a GP patient population. I recommend this article to be accepted with a few minor revisions:
Reply:
We thank the Reviewer for this comment.

1. In the abstract and background, I was initially confused at the description of the patient population. It is presented as "...patients with suspected COVID-19 managed by GPs (confirmed cases, no-COVID cases, and uncertain cases)...". I did not immediately understand that the patients suspect themselves of a COVID-19 infection who then present to a GP who ultimately determines the patient's COVID-19 status after ordering one of the three tests described in the methods. I suggest re-wording this definition slightly to clarify the cohort of patients used in this study.
Reply:
To take this comment into account, we have modified the Abstract and Background, as follows:

Abstract: “Outcome measures: Initial symptoms, COVID-19 status, persistent symptoms 3 months post-inclusion, and a composite criterion for potentially COVID-19-related events (hospitalization, death, emergency department visits). The final COVID-19 status (“confirmed”, “no-COVID”, and “uncertain” cases) was determined by the GP after the receipt of lab test results. “(page 2)

Background: “Therefore, the objectives of the present study were to (i) describe and compare the initial clinical characteristics of a cohort of patients with suspected COVID-19 managed by GPs and whose COVID-19 status (“confirmed”, “no-COVID” and “uncertain” cases) was determined by the GP after he/she had received lab tests results,”(pages 4-5)

2.In the methods, the description of how COVID-19 status was determined is concerning because the patients are all recruited between March and May of 2020 which is when both the RT-PCR and serology tests were not widely available. As a reader, this called into question how the patients were grouped into confirmed COVID, no COVID, and uncertain COVID, even with the caveat that serology tests were administered a posteriori. Please include a description or table showing how many patients had each test for COVID-19, whether they were positive or negative, and what subgroup they were assigned to.
Reply:
We have added the requested information as supplementary Table S2, which we cite in the Results section page 9.

3.The first line of the discussion is misleading: "During the first wave of COVID-19 in France....". It suggests that all patients in France with suspected COVID-19 were included in the study. Please reword for clarity in relation to study that was performed.
Reply:
We agree with the Reviewer and have clarified this sentence, as follows: “We included 516 patients managed by GPs for suspected COVID-19 during the first wave of the disease in France: 32.2% were classified as “confirmed COVID” cases, 34.9% were classified as “no-COVID” cases, and 32.9% were classified as “uncertain COVID” cases.” (page 11)

VERSION 2 – REVIEW

REVIEWER	Nehme, Mayssam Hôpitaux Universitaires de Genève, Primary Care Division
REVIEW RETURNED	19-Mar-2023

GENERAL COMMENTS	The authors have addressed all the concerns in their review.